# THE MEDICAL LETTER

## on Drugs and Therapeutics

blished by Drug and Therapeutic Information, Inc., 136 East 57th Street, New York 22, N. Y. Vol. 1, No. 5 March 20, 1959


## ORINASE AND DIABINESE

"Breakthrough in Diabetes" is the way Upjohn speaks of its drug, Orinase (tolbutamide). No one will quarrel with the description. Although it has been known since 1942 that sulfonylurea compounds could produce hypoglycemia in normal subjects, it was not until Orinase was introduced in 1957 that many patients were able to free themselves of insulin injections and control their diabetes with this oral drug.

Despite extensive clinical experience, its mode of action is not clear. It is ineffective in the absence of insulin (in depancreatized animals and in severe or juvenile-type diabetes). It is not strictly a substitute for insulin although its use may obviate the need for insulin in many diabetics. Nor is dosage of the drug related to the requirement for insulin. Small doses can replace moderate insulin doses in some patients, but no amount will replace even small insulin doses in others. Increasing the dosage augments the effect on carbohydrate metabolism only up to a kind of "ceiling," while resistant cases fail to respond to any dose.

WHERE ORINASE IS USEFUL - Many patients who develop mild, stable diabetes in middle or late life can control the disease by diet alone; others with essentially mild diabetes have been unable to control hyperglycemia and glycosuria without insulin. It is with these latter patients that the drug is most useful. It rarely helps patients with diabetes of juvenile onset, those with unstable diabetes, or those in whom the condition is so severe that they develop ketosis when insulin is withdrawn. In any case, actual trial under careful observation is necessary to determine whether Orinase can be used in place of insulin. Patients regulated on insulin may be safely tried on Orinase if the urine is tested frequently for acetone. Failure to return to insulin promptly if acetonuria develops has resulted in many instances of severe acidosis. Some feel that the drug is a helpful adjunct to insulin for the control of the "brittle" diabetic; no controlled experiment supporting this belief has, however, been reported.

Orinase has thus far produced little or no serious toxicity. Skin reactions (pruritus, erythema, urticaria and purpura) and gastrointestinal reactions (bloating, nausea and constipation) have been noted in about three per cent of reported cases, though often the reactions have not been severe enough for the drug to be stopped. Since the drug may be required over a lifetime, it is too early to judge its ultimate toxicity. Certainly the claim that Orinase is "even safer than aspirin" is not justified. The effect of the drug on the degenerative, vascular changes which occur in diabetes also cannot be evaluated until after many years of care-


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fully controlled clinical studies. There are still enough questions unanswered to make inadvisable the use of the drug by patients who can be controlled by diet alone or who are content to remain on insulin.

DOSAGE OF ORINASE - Orinase is generally given in doses of 0.5 to 2 Gm. daily. It is excreted rapidly (its half-life is 5 to 8 hours), a single dose being almost completely eliminated in 24 hours. There is no evidence that raising a single dose above 1.5 Gm. will give an augmented response, but added doses in the latter part of the day may improve 24-hour control (Baird and Duncan, Scottish Med. J., 2:341, '57). Many mild cases require only 0.5 to 1 Gm. before breakfast. It is rarely helpful, and it is probably inadvisable, to exceed a maintenance dosage of 1 Gm. before breakfast and again before supper. An initial dosage of 1 Gm. three times daily is, however, recommended when the attempt is made to substitute Orinase for insulin (with prompt reversion to insulin if acetonuria develops). In mild cases which have not been on insulin, one may start with 1 Gm. before breakfast without a priming dose, readjusting as necessary after a few days by reducing the morning dose or by adding a supper dose. Orinase may occasionally provoke mild hypoglycemia symptoms, despite the manufacturer's claim to the contrary.

DIABINESE - The new antidiabetic drug, chlorpropamide (Diabinese-Pfizer) is said to afford a "stronger" hypoglycemic effect than Orinase. There is no good evidence, however, that Diabinese is more effective where Orinase has been given in divided doses. The drop in blood sugar in diabetic patients during the first several hours after initial dosage with Diabinese does not differ significantly from that after an equal dose of Orinase (A. M. Tornow, et al., Diabetes, 8:1, Jan.-Feb. '59). The impression that Diabinese has greater strength results from the fact that it is excreted very slowly (its half-life is 36 hours); it therefore acts through a longer interval, and is cumulative even when taken only once daily. Although it is effective in a single daily dose, about 20% smaller than that of Orinase, severe toxic reactions have been encountered with Diabinese (jaundice and liver injury; thrombocytopenia and exfoliative dermatitis). It is too early to judge the incidence of such reactions. A number of instances of severe toxic reaction were noted at the September, 1958 symposium on Diabinese at the N. Y. Academy of Science, and other cases have been cropping up since that time. Whatever the incidence, the toxicity of Diabinese is clearly much greater than that of Orinase, and it seems highly inadvisable to substitute Diabinese for Orinase. The convenience of taking Diabinese only once daily is hardly worth the added risk.

## ILOSONE

Despite its newness, erythromycin propionate (Ilosone-Lilly) appears to be a valuable addition to the list of important antibiotics. Ilosone is a propionyl ester of erythromycin intended only for oral administration. The limited experience thus far indicates that it is superior to the older erythromycin.

Erythromycin is a broad-spectrum antibiotic effective against such gram-positive coccal organisms as pneumococci, Beta hemolytic streptococci and staphylococci, and against a number of gram-negative bacteria, such as meningococci,

gonococci, Hemophilus influenzae and Hemophilus pertussis. About 80 per cent of coagulase-positive strains of Staphylococcus aureus are susceptible to its action (Schneierson, S. S., J. of Mt. Sinai Hosp., 25:52, Jan.-Feb. '58).

ILOSONE'S ADVANTAGE - Erythromycin produces relatively low blood levels, however. With the adult dosage of about 2 Gm. daily often required for severe infections, gastrointestinal irritation (as evidenced by nausea, cramping, abdominal pain and diarrhea) is fairly frequent, even if the antibiotic is enteric-coated. These side effects are apparently related to dosage, and lowering the dosage usually alleviates the symptoms. The advantage of Ilosone is that oral administration produces blood levels about three times as high as the same oral dosage of erythromycin. Moreover, peak levels are reached earlier and persist longer.

The two forms of erythromycin are similar in antibacterial spectrum; the minimum inhibiting concentration needed to prevent the growth of any sensitive bacterial strain is practically the same for both forms. There is also complete cross resistance between the two; therefore nothing is to be gained by using either one to combat an organism which has been found resistant to the other.

Since Ilosone has been used for a relatively short time, the judgment that it is comparable to the older erythromycin in freedom from toxicity and serious side effects must be tentative. In view of the higher and more prolonged blood levels achieved with the propionate, however, it should be possible to achieve satisfactory clinical results with fewer gastrointestinal reactions by giving smaller doses at longer intervals. Only more experience can determine optimum dosage schedules. Better absorption and higher blood levels result when Ilosone is taken about two hours before meals.

## TEMARIL

Trimeprazine (Temaril-SKF) is promoted as an oral remedy "for the relief of itching - regardless of cause." In view of the great number of causes of this symptom, and the vast number of sufferers who consider it a major ailment, a drug that would relieve itching regardless of cause would be a blessing indeed.

In the absence of controlled clinical trials to support the claim that "Temaril has been found effective in the relief of more than 70% of all cases of moderate and severe itching - regardless of cause," there is no way of judging the validity of the claim. Many drugs offered for the relief of itching have some limited effectiveness, but there is still a place for the universal remedy that will soothe the itchy scalp, the itchy anus or the itchy foot, that will be effective in acute and chronic dermatoses and in psychogenic itches, and that will give relief not briefly, but for hours. Temaril is apparently effective in some cases; whether it is more effective than other antihistamines, a sedative dose of barbiturate, or, in some patients, a placebo, has yet to be demonstrated. Since mild drowsiness was reported as a side effect in some 60% of patients treated with Temaril, whatever effectiveness it has is probably due to its sedative property rather than to any specific antipruritic action. Less frequently occurring side effects include

skin disorders and allergic reactions such as giant urticaria, as well as nervous agitation.

Of immediate concern is the question of whether Temaril should be used, even assuming that it is effective. Temaril is a phenothiazine antihistaminic agent, closely related chemically to Thorazine, Sparine, Compazine, and Phenergan. Although the suggested minimum adult dose of Temaril (5 mg.) is small, daily dosage as high as 80 mg. is suggested for some patients. The possibility that Temaril, particularly when taken in the larger dosages over a long period will display some of the serious toxic and side effects of the phenothiazine drugs, such as jaundice, hypotension, parkinsonism, convulsions and blood dyscrasia, cannot be overlooked. The Feb. 19th issue of The New England Journal of Medicine reports a case of agranulocytosis caused by Temaril, in the moderate dosage of 20 mg. per day for about 50 days. In the light of this and other recent reports of severe toxic reactions to phenothiazine drugs, physicians may prefer to employ potentially less toxic remedies than Temaril for a symptom such as pruritus.

## FOLLOW-UP ON DEXAMETHASONE

Commenting on reports that dexamethasone (Decadron-Merck; Deronil-Schering) has fewer and milder toxic and side effects than older adrenal steroids, the first issue of The Medical Letter (1/23/59) advised against the acceptance of such early reports, and said: "...with the passage of enough time the usual side effects are likely to appear." A new report (Slater, J. D. H., et al., Lancet, 1: 173, 1/24/59) supports The Medical Letter's caution. A detailed study of eight patients showed that dexamethasone produced potassium and nitrogen losses and exacerbation of glycosuria in diabetes, much as with other adrenal steroid compounds. The authors comment, "It is certainly premature to claim that it will be less likely to cause unpleasant side effects."

Even though serious side effects have not been overcome with the successive new corticosteroids, however, both physician and patient benefit from having a number of different preparations available. These steroids - prednisone, prednisolone, methylprednisolone, triamcinolone and dexamethasone - do afford a variety of forms to which patients may not respond entirely alike. When a patient is doing poorly with one drug, another may turn out to be more useful (or less injurious) for that patient.

When The Medical Letter checked the comparative prices of Decadron and other steroids in a number of New York drug stores in January, it found Decadron selling for about the same price as the others. A further check in early March shows that while some drug stores are charging the same price for all of the newer corticosteroids, some are selling both Decadron and Deronil for less than the others, the difference ranging from $1 to several dollars less for a hundred tablets of equivalent dosage. In view of the cost of steroid therapy, particularly for conditions requiring high and prolonged dosage, the saving in some drug stores is great enough to make dexamethasone the drug of choice for many patients even if it has no therapeutic advantage over the other drugs.

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS is published fortnightly by Drug and Therapeutic Information, a non-profit corporation, 136 E. 57th St., New York 22, N. Y. Second-class postage paid at New York, N. Y. The subscription fee is $12.50 per year ($6.25 for residents, internes and students).